Research Article

Fast and Convenient Synthesis of Amine-Terminated Polylactide as a Macroinitiator for ω-Benzyloxycarbonyl-L-Lysine-N-Carboxyanhydrides

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Amine-terminated poly (L-lactide) (NH_2-PLLA) with various chain lengths were successfully synthesized by sequential tert-butyl-N-(3-hydroxypropyl) carbamate initiated bulk ring-opening polymerization (ROP) of L-lactide (L-LA) in the presence of Stannous(II) 2-ethylhexanoate ($Sn(Oct)_2$) and deprotection of the N-*tert*-butoxycarbonyl (Boc) group at the end of the polymer chain. The polymers obtained were characterized by FT-IR, ^{1}H NMR, and GPC method. NH_2-PLLA thus prepared was used to initiate the polymerization of ω-benzyloxycarbonyl-L-lysine-N-carboxyanhydride (Lys (Z)-NCA), and the result confirmed the high nucleophilicity of the terminal amine group. This method was not only suitable for the preparation of low molecular weight NH_2-PLLA, but also quite efficient in the synthesis of high molecular weight samples.

1. Introduction

During the last few years, aliphatic polyesters based on hydroxyalkanoic acid, such as polylactides (PLLA), polyglycolide (PGA), poly (caprolactone) (PCL), and their copolymers have become the most important biopolymers because of their biodegradability and good biocompatibility for pharmaceutical and biomedical applications. However, the scope of further application of PLLA is limited for the lacking of highly reactive groups as triggers of chemical reaction, and the surface of PLLA is very hydrophobic [1]. Chemical modification, especially end functionalization, is an important method to expand the applications area of these polymers [2]. The end-functionalized polymers are also important intermediates which can react at the end of the chain with other molecules containing reactive groups such as acid chlorides, sulfonyl chlorides, acid anhydrides, and activated esters for the synthesis of novel polymeric materials [3, 4]. NH_2-PLLA can be used to conjugate with lactose to form a new bioabsorbable material which shows high biodegradability and gives a microphase separation structure [1]. Especially, they were investigated as a macroinitiator for the ring-opening polymerization (ROP) of amino acid N-carboxyanhydrides (NCAs) to prepare a block copolymer containing polypeptide segments which showed quite different properties from other polymers [5–14].

The synthesis of NH_2-PLLA was based on a method first reported by Gotsche et al. in 1995 [5]. The main idea of his point was capping the hydroxyl end group of PLLA with BOC-L-Phe which containing a protective amino group using N,N′-dicyclohexylcarbodiimide (DCC) as the condensing agent. However, conversion of the hydroxyl group into an N-protected amino acid ester with the acylation of DCC is always not sufficient, possibly because of the low reactivity of the terminal hydroxyl group and the steric hindrance of the huge polymer chain [7]. Fan et al. [8] synthesized a mixed acid anhydride of BOC-L-Phe and trimethylacetyl chloride (TMAC) to improve the reactivity of the coupling agent. The complete end capping of the end hydroxyl group of PLLA was achieved by reacting with the mixed acid anhydride under the existence of 4-(1-pyrrolidinyl) pyridine. Finally, the protective group was removed to form the free amino group at the chain end of PLLA. Caillol et al. [6] synthesized amino-functionalized PLLA through
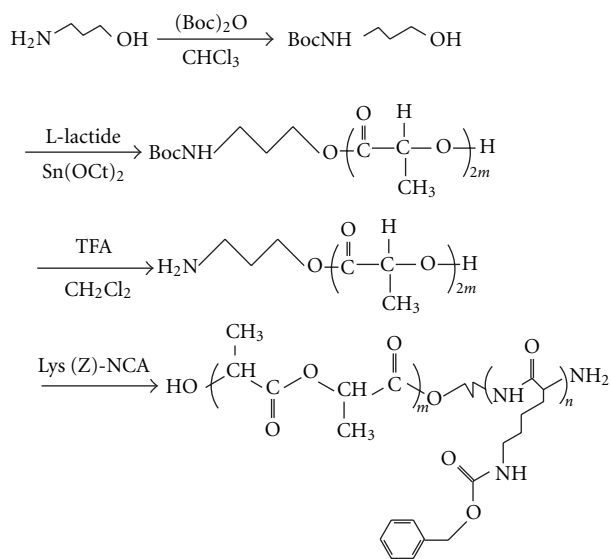
FIGURE 1: Synthesis of NH$_2$-PLLA and PLLA-b-PZLys block copolymer.

ring-opening polymerization of L-LA initiated by zinc alkoxide that was obtained from the reaction between diethylzinc and tert-butyl-N-(3-hydroxypropyl) carbamate. Lately, Ouchi et al. [1] synthesized NH$_2$-PLLA through anionic ROP of L-LA in dry tetrahydrofuran using Boc-amino-OK as an initiator. But in our opinion, the initiators mentioned above were so sensitive to environmental factors such as humidity and oxygen that they were so difficult to handle and store.

Stannous(II) 2-ethylhexanoate (Sn(Oct)$_2$) is one of the most widely used compounds for catalyzing the ROP of various lactones and lactides [15–18]. Despite the fact that the mechanism and the initiating complex remain unclear, both mechanisms are thought to be alcohol initiated [19–23], since the degree of polymerization is clearly dependent on the monomer-to-alcohol ratio [24], and the end groups of the polymers have hydroxyl functionalities. In the present research, we proposed a novel three-step method to achieve the complete end capping of PLLA with amine group by tert-butyl-N-(3-hydroxypropyl) carbamate initiated bulk ring-opening polymerization of L-LA catalyzed by Sn(Oct)$_2$. In order to control the molecular weight, alcohols have been widely used to initiate the bulk ring-opening polymerization of L-LA, but to our knowledge, the synthetic method of NH$_2$-PLLA initiated by tert-butyl-N-(3-hydroxypropyl) carbamate under the catalyzing of Sn(Oct)$_2$ has not been published. The outline of the synthetic route is illustrated in Figure 1. At first, the amine group of 3-amino-1-propanol was protected by reaction with di-tert-butyl dicarbonate under the existence of triethylamine. Then, tert-butyl-N-(3-hydroxypropyl) carbamate synthesized above was used to initiate the polymerization of L-LA to prepared Boc-amino terminated PLLA (BocNH-PLLA). Finally, the Boc group at the chain end was removed by the treatment of trifluoroacetic acid. The synthesized NH$_2$-PLLA (NH$_2$-PLLA) was used as a macroinitiator for the ROP of Lys (Z)-NCA to

prepare the block copolymer of L-lactide and ω-benzyloxycarbonyl-L-lysine (PLLA-b-PZLys).

2. Experimental

2.1. Materials. L-LA was purchased from PURAC and recrystallized twice from anhydrous ethyl acetate. Anhydrous trifluoroacetic acid (TFA), Sn(Oct)$_2$ were from Sigma and distilled twice before use. Di-tert-butyldicarbonate, triphosgene, and ω-benzyloxycarbonyl-L-lysine were purchased from GL biochemical of Shanghai and used as received. Lys (Z)-NCA was prepared according to the previously method [25]. The purity of the obtained NCA was checked by DSC analysis from the position and the shape of the melting process. The melting endotherm of Lys (Z)-NCA was about 100°C-101°C with a highly asymmetric peak, showing the absence of residual chloride. Other reagents were commercially available and used as received. All solvents were thoroughly dried and distilled before use.

2.2. Synthesis

2.2.1. Synthesis of Tert-Butyl-N-(3-Hydroxypropyl) Carbamate. 3-amino-1-propanol (1.52 g, 20 mmol) and triethyamine (2.22 g, 22 mmol) were dissolved in chloroform (50 mL) in a flask equipped with a magnetic stirrer, and di-tert-butyldicarbonate (4.8 g, 22 mmol) in chloroform (20 mL) was added dropwise to the solution in 1 h with continuous stirring. After reaction for another 1 h, the concentrated solution was diluted with 5% potassium hydrogen sulfate aq. Soln. and extracted with ethyl acetate and dried over MgSO$_4$. After filtration and evaporation of the solvent, purification of the compound was carried out by column chromatography on silica gel using ethyl acetate and hexane as eluent. The purity of tert-butyl-N-(3-hydroxypropyl) carbamate obtained as colorless viscous oil was found to be over 98.7% by HPLC analysis. Yield: 86.2%.

2.2.2. Preparation of BocNH-PLLA, PLLA$_{25}$. PLLA was synthesized by ROP of L-LA initiated by tert-butyl-N-(3-hydroxypropyl) carbamate and catalyzed by Sn(Oct)$_2$. L-LA (14.4 g, 100 mmol) and tert-butyl-N-(3-hydroxypropyl) carbamate (700 mg, 4 mmol) were weighted in a glove box and introduced in an oven-dried schlenk bottle, and 72 mg of Sn(Oct)$_2$ (0.5 of L-LA) was added as a 0.02 g/mL solution in dry dichloromethane. After vacuumized and purged with Ar three times, the bottle was degassed under a high vacuum for 2 h to remove the residue dichloromethane. The bottle was then flame-sealed and immersed in a 130°C oil bath for 6 h. The obtained white solid was dissolved in dichloromethane, and the catalyst Sn(Oct)$_2$ was removed by precipitating the polymer solution in a large amount of chilled methanol, filtered and dried in vacuum at room temperature. The polymer was recovered over 85% yield with a stannous content less than 20 ppm.

2.2.3. Synthesis of Amine-Terminated PLLA. 1 g of PLLA was introduced in a flask which has been dried, purged with Ar
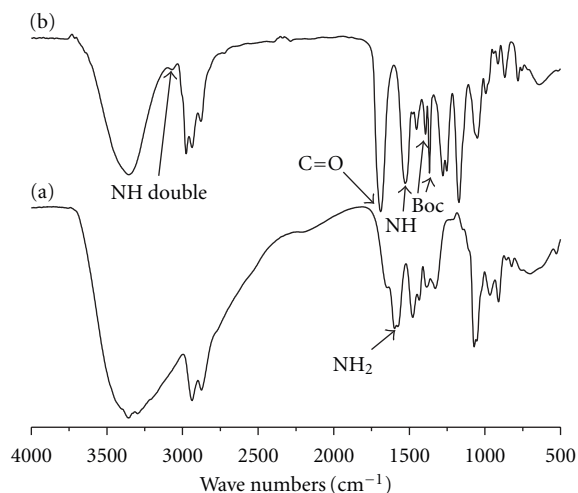
FIGURE 2: FT-IR spectra of 3-amino-1-propanol (a) and tert-butyl-N-(3-hydroxypropyl) carbamate (b).

FIGURE 3: ^{1}NMR spectra of BocNH-PLLA in CDCl$_3$.

and vacuumized several times. Freshly distilled methylene chloride (12 mL) was added, followed by a large excess of anhydrous trifluoroacetic acid (6 mL). The solution was stirred at room temperature for 1 h, after which time all solvents were evaporated, the polymer was redissolved in dichloromethane and washed with aqueous NaHCO$_3$ (5%) and water and finally dried over MgSO$_4$. After filtration, the solution was precipitated in chilled methanol and dried in a vacuum at room temperature. The polymer was recovered over 80% yield.

2.2.4. Synthesis of PLLA-b-PZLys Block Copolymer. 2 g (6.5 mmol) or 5 g (16.3 mmol) of Lys (Z)-NCA was dissolved in 50 mL of CH$_2$Cl$_2$. The resultant solution was added to a solution of NH$_2$-PLLA$_{25}$ (1 g, 0.27 mmol) in 15 mL CH$_2$Cl$_2$. The reaction mixture was stirred under an inert atmosphere for 24 h at room temperature. The viscous solution obtained was poured into a large quantity of chilled diethyl ether, followed by filtration and drying under reduced pressure to give a white powder over 90% yield.

2.2.5. In Vivo Tissue Responses. Boc-PLLA (DP$_{LA}$ = 100), NH$_2$-PLLA (DP$_{LA}$ = 100), and PLLA-*b*-PZLys (DP$_{LA}$ = 25, DP$_{ZLys}$ = 24) were dissolved in CH$_2$Cl$_2$ at a concentration of 10% (w/v) in the watch glass. Polymer films were obtained by evaporating the solution under room temperature and dried in vacuum for 3 days. Nude rats weighing 200–250 g were implanted with the polymer films (n = 4 for each polymer) in legs. Animals with polymer films were allowed to survive 28 days after implantation and then terminated. The surgical wounds were reopened, and the leg musculature was removed with the polymer remnant and fixed in 10% formalin for histological analysis. Specimens were prepared for H-E staining analysis.

2.3. Measurements. ^{1}H-NMR spectra were recorded at room temperature on a Bruker DRX-500 using CDCl$_3$ as the solvent. Gel permeation chromatography (GPC) was carried
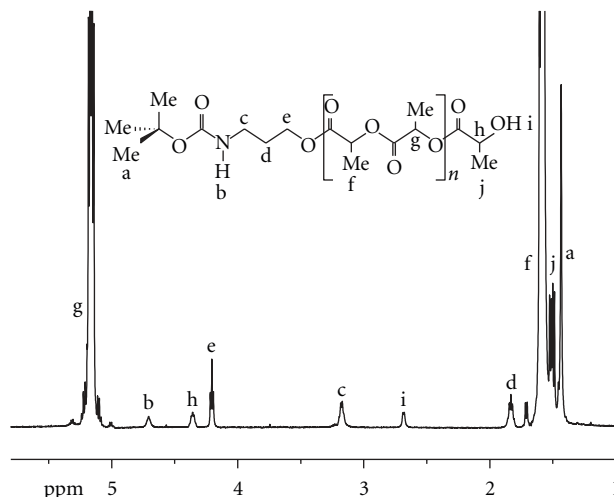
out on a Waters HPLC system equipped with a Model 2690D separation module, a Model 2410 refractive index detector, and Shodex columns (K802.5, K803, and 805). Chloroform was used as eluent at the flow rate of 1.0 mL/min. Calibration was fulfilled with narrow-molar-mass distributed polystyrene standards. The infrared spectral analysis of the samples was performed on a FT-IR spectrophotometer (Nicolet Magna-IR550).

3. Result and Discussion

The general synthetic routes for the preparation of tert-butyl-N-(3-hydroxypropyl) carbamate, BocNH-PLLA, NH$_2$-PLLA, and PLLA-*b*-PZLys were shown in Figure 1.

3.1. Synthesis of Tert-Butyl-N-(3-Hydroxypropyl) Carbamate. Boc was chosen as the protective group for amine group of 3-amino-1-propanol because of its stability under the designed temperature of polymerization of L-LA and it can be easily removed under mild conditions. Tert-butyl-N-(3-hydroxypropyl) carbamate was obtained from the reaction of 3-amino-1-propanol and di-tert-butyldicarbonate at room temperature under the existence of triethylamine. The complete protection of the amine group was confirmed by IR spectra (Figure 2). The absorption peak at 1649.0 cm^{-1} assigned to primary amine was completely disappeared in tert-butyl-N-(3-hydroxypropyl) carbamate, and the peaks at 1527.0 cm^{-1} (ν_{CO-NH}) and 1689.6 cm^{-1} (ν_{CO}) were attributed to second amide, indicating the successive protection of amine group by *t*-butoxycarbonyl. The peaks at 1366.7 cm^{-1} and 1392.8 cm^{-1} belonged to the Boc group were also characteristic of the formation of tert-butyl-N-(3-hydroxypropyl) carbamate.

3.2. Synthesis of NH$_2$-PLLA. Amino-functionalized PLLA was synthesized through ROP of L-LA with tert-butyl-N-(3-hydroxypropyl) carbamate. The bulk polymerization can be easily carried out at 130°C because of the stabilization of
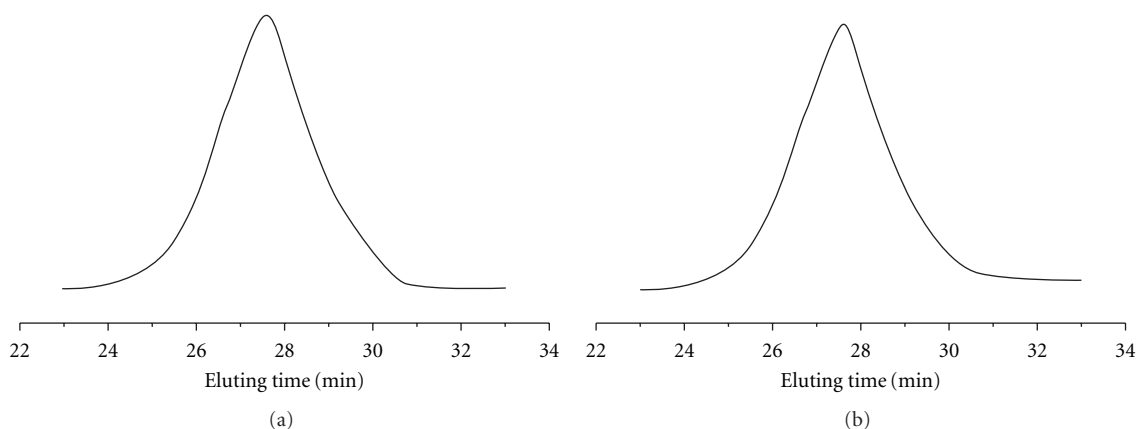
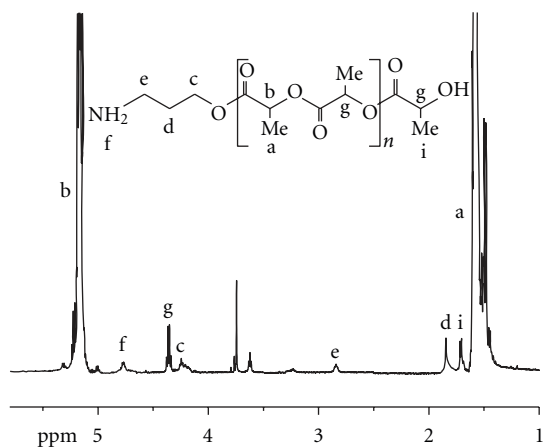Figure 4: GPC curves of BocNH-PLLA (a) and NH$_2$-PLLA (b).
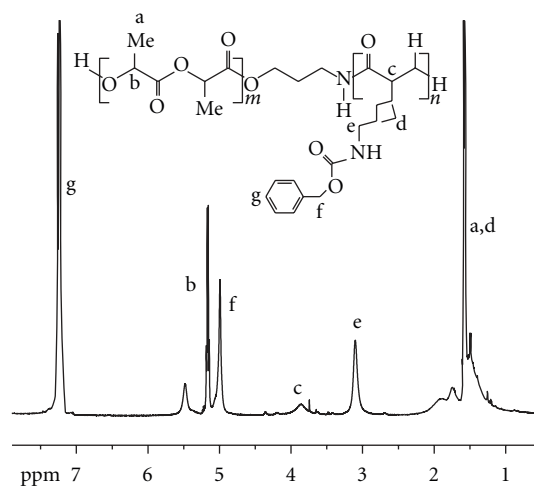

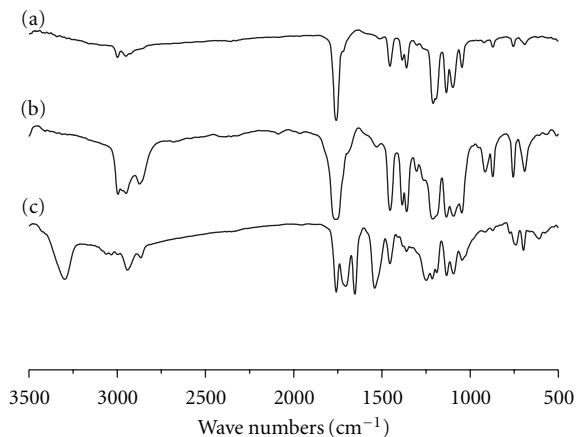Figure 5: ^{1}H NMR spectra of NH$_2$-PLLA in CDCl$_3$.

Figure 6: FT-IR spectra of BocNH-PLLA (a), NH$_2$-PLLA (b), and PLLA-*b*-PZLys (c).

Figure 7: ^{1}H NMR spectra of the block copolymer of PLLA-*b*-PZLys.
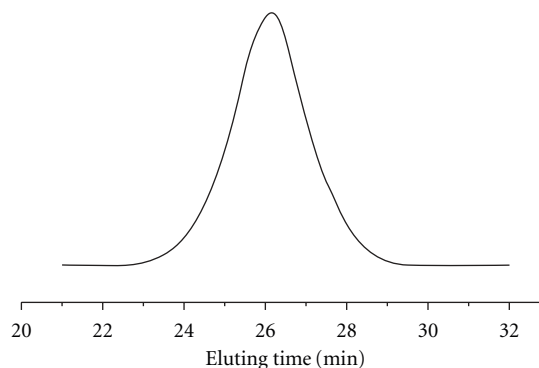
Figure 8: GPC trace of the block copolymer of PLLA-*b*-PZLys.

Boc group under this temperature in 12 h with high yields in recovered polymer between 85% and 98%. In this study, the polymerization of L-LA was carried out under rigorously anhydrous conditions to avoid any initiation of water, which will lead to a mixture of carboxyl acid terminated PLLA and BocNH-PLLA. The degree of polymerization of BocNH-PLLA was found to be easily controlled by changing the feed molar ratio of L-LA to tert-butyl-*N*-(3-hydroxypropyl) carbamate. The characteristics of the synthesized polymers are reported in Table 1.

FIGURE 9: *In vivo* biocompatibility of the polymer films (interface surfaces are denoted by arrows).
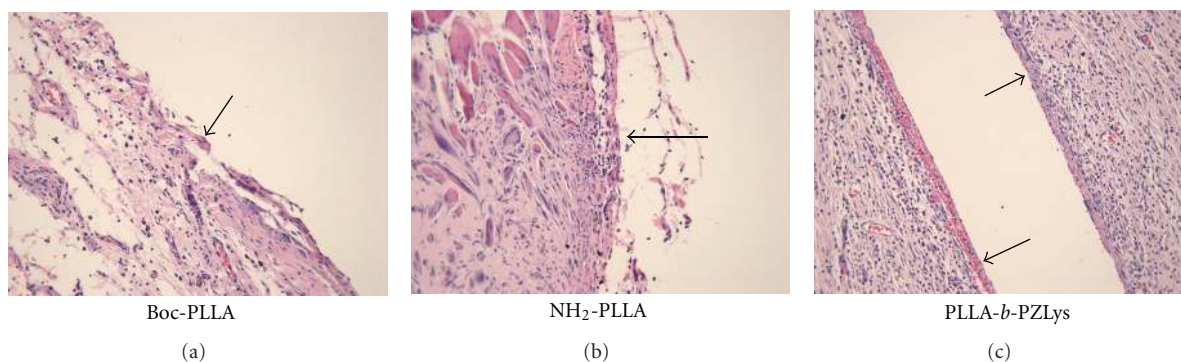
TABLE 1: Molecular weight characterization of BocNH-PLLA homopolymers.

Sample	M_0/I_0 (mol)	Mn[a]	Mn[b]	Mn[c]	PDI	Mn[d]	Mn[b]/Mn[d]
PLLA$_{10}$	10	1440	1544	2680	1.21	1527	1.01
PLLA$_{25}$	25	3600	3487	6423	1.24	3661	0.95
PLLA$_{50}$	50	7200	7663	13848	1.52	7893	0.97
PLLA$_{100}$	100	14400	15295	28657	1.48	16334	0.94
PLLA$_{150}$	150	21600	22927	39569	1.46	22554	1.02
PLLA$_{200}$	200	28000	33295	55436	1.61	31599	1.05

[a]Calculated from the free ratio. [b]Calculated from the ^{1}H NMR (see Figure 2). [c]Obtained from GPC based on the PS calibration. [d]Corrected GPC result, Mn[c] $\times$ 0.57.

The functionality of the end group of the polymer was determined by comparing the molecular weight obtained from GPC and that determined by ^{1}H NMR [6] using the signals of a, c, or e attributed to the end group and that of lactide units g or f (Figure 3). In all cases, the functionality was found close to 1, which means that all polymer chains were capped with BocNH groups. The GPC trace of the resulted polymer (Figure 4(a)) is a single peak, and the molecular weight distribution of the product is narrow, showing that only one type of polymer corresponding to the expecting end group.

The next step removal of the Boc group of the terminal residue from the obtained polymer was realized by treatment in the mixed solvent of TFA and CH$_2$Cl$_2$ at room temperature for 1 hour. This reaction deprotected all primary amine functions at the end of the polymer, without lowering the molecular weight, as shown by the GPC trace (Figure 4(b)). This was also confirmed by ^{1}H NMR (Figure 5) with the complete disappearance of methyl peak at 1.43 ppm corresponding to the terminal Boc group. The signal of –CH$_2$–N shifted from 3.16 to 2.75 ppm. The ratio between this peak and that of lactide units (a and b) remained also constant after the deprotection, showing the degree of polymerization not changed.

3.3. Block Copolymerization. It is well known that primary amines, being more nucleophilic than basic, can be used to initiate the ROP of NCAs to prepare polypeptide containing block copolymers. Among all polypeptides, poly (L-lysine) (PLL) is unique due to its hydrophilicity and functional side NH$_2$ groups which can help to improve the affinity

to proteins and cells, or to ionically combine with drugs, antibodies or DNAs, and thus may lead to breakthrough in fields of targeting drug delivery and gene delivery [26, 27]. Therefore, in order to test the reactivity of the amine-terminated polymer prepared above, NH$_2$-PLLA was used as a macroinitiator for the ROP of lys (Z)-NCA. FT-IR spectra of BocNH-PLLA, NH$_2$-PLLA, and PLLA-*b*-PZLys were illustrated in Figure 6. The absorption at 1758 cm^{-1} belong to the carbonyl group, 1951 cm^{-1} to methyl, and 1046 and 1098 cm^{-1} to C–O–C bond. In the spectrum of the block copolymer, two amide I bands at 1653 cm^{-1} and 1704 cm^{-1} were observed, most likely for the main chain amide linkage and the side amide group, respectively. The amide II band was also observed at 1540 cm^{-1}.

Figure 7 illustrates the ^{1}H NMR spectra of the block copolymer. Besides the signals of PLLA, new peaks at about 7.23, 4.96, 3.85, and 3.03 ppm corresponding to the lysine residue appeared. From the integral ratio of lactide unit to lysine unit, the average degree of polymerization (DP) of the polypeptide block can be easily calculated to be 21 and 53, which is very close to the feed molar ratio of NCA monomer to the macroinitiator, confirming the high initiation reactivity of NH$_2$-PLLA. The GPC trace of the resulting copolymer (Figure 8) showed a unimodal shape. This further indicated complete amine-end-capping of PLLA, and the copolymerization was completed successfully, and there was no homopolymer in the copolymer.

3.4. In Vivo Tissue Responses. The *in vivo* biocompatibility of Boc-PLLA, NH$_2$-PLLA, and PLLA-*b*-PZLys was evaluated via implantation of the polymer films in rats (Figure 9).

The polymeric implants and surrounding tissues were collected at day 28. Despite the difference in molecular weight and structures, there was no significant difference in inflammatory reactions between the polymers as assessed by fibrotic band thickness and lymphocytes infiltration, as shown in Figure 9. The three polymer films caused same fibrotic band thickness and the surrounding tissues showed an abundant perivascular infiltration of lymphocytes, which was most probably caused by the degradation of the polymer films.

4. Conclusion

Compared to the methods that have been published, a novel, very simple, and highly efficient approach for the synthesis of amine-terminated polylactide (may also be used for other kinds of polylactones and polylactides) with various chain lengths based on tert-butyl-N-(3-hydroxypropyl) carbamate initiated bulk ring-opening polymerization has been developed and shown to be successful. The deprotection of the Boc group can be easily carried out under mild condition without breaking up of the polymer chain. This method was confirmed not only suitable for the preparation of low molecular weight NH$_2$-PLLA, but also quite efficient in the synthesis of high molecular weight samples.
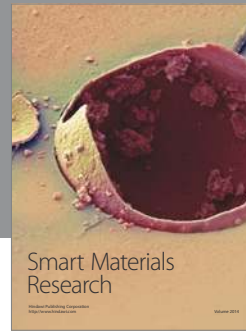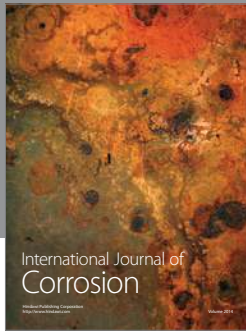
Acknowledgment

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